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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,735	05/19/2006	Ofer Mandelboim	2488.033	7654

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EXAMINER	
HAMUD, FOZIA M	
ART UNIT	PAPER NUMBER
1647	
MAIL DATE	DELIVERY MODE
12/01/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,735	MANDELBOIM ET AL.	
	Examiner	Art Unit	
	FOZIA M. HAMUD	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27,34-48* is/are pending in the application.

4a) Of the above claim(s) *12-19 and 34-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,20-27,47 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/20/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1a. Receipt of Applicants' amendment and arguments, filed on 20 July 2009 is acknowledged.

Status of Claims:

1b. Claims 28-33 have been cancelled. Claims 12-19 and 34-46 stand withdrawn. Thus claims 1-11, 20-27 and 47-48 are pending and under consideration.

Specification:

2. The amendment filed on 20 July 2009 properly describing all the panels of figures 2, 3, 5, 8, 9 and 10 is noted. No new matter has been added.

Priority:

3. The current application is a national stage entry of PCT/IL04/00583, international filing date of 30 June 2004, which claims priority from provisional Application 60/483,107, filed 06/30/2003. Thus, the filing date of 06/30/2003 is used for the purposes of applying prior art.

Response to Applicants' arguments:

4. The following objection and rejections are withdrawn in light of Applicants' arguments:

I. The objection to claims 1 and 4 is withdrawn. Claim 1 now ends with a period and claim 4 is clear.

II. The provisional rejection of claims 1-3, 47, 24 made on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5,

12 of copending Application No. 10/580,428, ('428) is moot, because the '428 application is now abandoned.

III. The rejection of claims 1-3, 24-27 made under 35 U.S.C. 102(b) as being anticipated by Mandelboim et al, (WO 02/08287, published on 31 January 2002), is withdrawn, because Mandelboim et al reference does not disclose a peptide fragment comprising a linker peptide connecting the ECD to the TM, wherein the peptide fragment is about 10-100 amino acid residues in length, as recited in amended claim 1.

IV. The rejection of claims 1-3 made under 35 U.S.C. 102(b) as being anticipated by Cantoni et al, (the Journal of experimental medicine, 1999, Vol. 189, No. 5, pp. 787), because Cantoni et al reference does not disclose a peptide fragment comprising a linker peptide connecting the ECD to the TM, wherein the peptide fragment is about 10-100 amino acid residues in length, as recited in amended claim 1.

V. Applicants' amendment has overcome the rejection of claims 20-27 and 47-48 made under 35 U.S.C. 112, second paragraph.

Maintenance of previous Rejections:

Non-Statutory double Patenting:

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. The rejection of claims 20-23 made on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 4, of copending Application No. 10/538,231, is maintained. Applicant's intension to file appropriate Terminal Disclaimer upon allowance of the subject matter of the current application or that of application copending Application No. 10/538,231, whichever occurs first, is acknowledged.

Claim Rejections - 35 U.S.C 112, first paragraph:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6a. The rejection of claims 1-11, 20-27, 47-48 made under 35 U.S.C. 112, first paragraph, for not enabling the full scope of the claimed invention is maintained for reasons of record as set forth in the office action mailed on 18 March 2009.

The specification while being enabling for an isolated NKp46D2 peptide fragment or a fusion protein comprising the natural cytotoxcity receptor NKp46 and the Fc portion of human IgG1, (NKp46-Ig), said molecules which bind to a viral infected cell or to a tumor cell, does not reasonably provide enablement for an isolated peptide fragment of

a natural cytotoxicity receptor of an NK cell, comprising a linker peptide connecting the extracellular domain of the receptor to the transmembrane portion of the receptor, wherein the isolated peptide fragment is about 10-100 amino acid residues in length and wherein said peptide fragment exhibits at least one activity selected from binding to a viral infected cell or binding to a tumor cell, as recited in amended claim 1 or a pharmaceutical composition comprising said peptide or a fusion protein comprising said peptide, other than the fusion protein of SEQ ID NOs:13-18.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, make and use the invention commensurate in scope with these claims.

At the outset, Applicants' arguments pertaining to NKp44 peptide fragments are not considered, because in the response to the restriction requirement, filed on 26 January 2009, Applicant elected the invention of Group I, which is drawn to an isolated peptide fragment comprising NKp46.

Applicant submits that the teaching in the specification of NKp46D2 substitution mutants and the ability of fusion proteins comprising those mutants to bind to target cells provides sufficient support for a fragment such as SEQ ID NO:3, which retains the desired binding activity. Applicant contends that Example 5 of the specification teaches that Ig-fusion proteins of the mutants NKp46T125A and NKp46N216A show levels of binding to viral infected cells that are substantially identical to that exhibited by NKp46D2 (compare Fig. 6 and Fig. 3a), whereas the mutants NKp46T225A and NKp46T225N (i.e. threonine replaced by alanine and asparagine, respectively), show

substantially reduced binding to the same cells. Thus, Applicant argues that the specification teaches that the amino acid residues at positions 125 and 216 are apparently non-essential for binding to viral infected cells and tumor cells, whereas residue 225 is essential for binding to viral infected cells and tumor cells. Applicant submit that the specification provides support that SEQ ID NO:3, corresponding to amino acid residues 215-254 of NKp46, including the essential amino acid residue at position 225 and even containing the non-essential residue at position 216, retains the desired binding activity. Regarding an "analog thereof", Applicant asserts that the specification teaches that an analog may have an amino acid sequence different from that of the specific molecule, such as when at least one amino acid residue is substituted.

These arguments have been considered, but are not found persuasive. The instant claims encompass an isolated peptide fragment of a natural cytotoxicity receptor of an NK cell, comprising a linker peptide connecting the extracellular domain of the receptor to the transmembrane portion of the receptor, wherein the isolated peptide fragment is about *10-100* amino acid residues in length and wherein said peptide fragment exhibits at least one activity selected from binding to a viral infected cell or binding to a tumor cell. However, the specification teaches that NKp46: D2 proximal which comprises 134 amino acid residues (residues 121-254 of the full length receptor of isoform a), binds viral infected cells or binding to a tumor cells. The specification further teaches that NKp46D1 (22-120), which the extracellular domain of NKp46, does not bind to viral or tumor cells, (see Example 6). However, the specification does not

teach that a fragment that comprises amino acid residues 121-254 of NKp46, (SEQ ID NO:3) retains the activity of binding to a viral infected cell or binding to a tumor cell. Thus, the specification does not teach a fragment comprising the amino acid set forth in SEQ ID NO:3 or analog that retains the desired activity. Applicant's argument that amino acid 225 is essential for binding, while amino acids 125 and 216 are not, is not disputed. However, the identification that amino acid 225 is essential for binding, while amino acids 125 and 216 are not, does not enable the claimed invention which encompasses a fragment that comprises at least 10-100 that retains the desired activity. It is noted that the claims are still drawn to a broad genus of peptide fragments/fusions. However, the specification fails to teach any isolated peptide fragment that retains the ability to bind to viral infected cell or tumor cells, other than an isolated NKp46D2 peptide fragment or a fusion protein comprising the natural cytotoxcity receptor NKp46 and the Fc portion of human IgG1, (NKp46-Ig). Undue experimentation would be required of the skilled artisan to design and generate all possible peptide fragments/fusions and analogs thereof which retain the desired activity.

Applicant argues that the specification provides an adequate teaching of how to make and use the composition of claims 24-27 directed to pharmaceutical compositions. Applicants submit that amended claim 47 encompasses various substitution mutations within D2 of NKp46 i.e at positions 125, 216 and 255. Applicants argue that the specification teaches point mutations in addition to those disclosed regarding position 225 and thereby provides support for the variant polypeptide of claim 47 as amended. Applicant moreover respectfully points out that claim 47 recites that the

amino acid substitution is "in an epitope required for recognition of viral infected or tumor cells", but the claimed variant polypeptide is not limited to one which exhibits such binding activity.

With regard to claim 48, the specification discloses that substitution of threonine at position 225 with serine resulted in decreased binding to viral infected cells but similar binding to tumor cells, thus the teaching in the specification of point mutations at position 225 in which threonine is substituted with any of serine, asparagine or alanine, provides adequate support for claim 48 as amended.

These arguments have been considered, but are not found persuasive. With respect to claims 24-27, which encompass “pharmaceutical composition", the specification must teach how to use the composition for at least one pharmaceutical use without undue experimentation for said claims to be enabled. To enable a pharmaceutical use for polypeptide of the claimed peptide fragment requires the specification to teach how to use the substance, without undue experimentation, for the prevention, diagnosis, alleviation, treatment or cure of a disease in the animal to which the substance is administered. However, the specification does not provide adequate guidance as to how the claimed peptide fragments can be used to treat any disorders, and undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. Due to the lack of direction/guidance presented in the specification regarding pharmaceutical use of the claimed polypeptide, the complex nature of the invention, the skilled artisan would not know how to use the invention recited in claims 24-27 in its full scope.

Regarding claims 47-48, the specification is enabling for a variant comprising the D2 of NKp46, wherein there are mutations at amino acid 225, 125 or 216. The specification teaches that amino acid 225 is essential for binding, while amino acids 125 and 216 are not. However, the specification does not teach a variant that comprises "an active fragment". Thus, while it is acknowledged that NKp46 variant with mutations at amino acid 225, 126 or 216 are enabled, "an active fragment thereof" recited in claim 47 is not enabled.

6b. The rejection of claims 1-11, 20-27 and 47 made under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such away as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, is maintained for reasons of record as set forth in the office action mailed on 18 March 2009. The specification fails to provide fragment that is about 10-100 amino acid residues in length and wherein said peptide fragment that exhibits at least one activity selected from binding to a viral infected cell or binding to a tumor cell, as recited in claims 1, 2; or "an analog" of the polypeptide that has the ability to bind viral infected cells or tumor cells, as recited in claim 1; or "an active fragment" with the desired activity, as recited in claim 47.

Conclusion:

7. No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Advisory Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to FOZIA M. HAMUD whose telephone number is (571)272-0884. The examiner can normally be reached on Monday-Friday: 8:00 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Art Unit 1647
17 November 2009

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